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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,061	10/04/2005	Tsuyoshi Morishita	00005.001277	3919

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EXAMINER	
WANG, CHANG YU	
ART UNIT	PAPER NUMBER
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,061	MORISHITA ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 38* is/are pending in the application.

4a) Of the above claim(s) *1-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/04/05, 12/02/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application Election/Restrictions

Applicant's election without traverse of Group V in the reply filed on November 20, 2006 is acknowledged.

Claims 1-19 and 38 are pending. Claims 1-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 20, 2006. Claim 38 is under examination in this office action.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a translation of the foreign application should be submitted under 37 CFR 1.55 in reply to this action.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology

often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Claim Objections

Claim 38 is objected to because of the following informalities: Applicant is required to spell out GSK-3 at the first usage. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 38 is rejected under 35 U.S.C. 112, first paragraph, while being enabling for enhancing neurogenesis of Tuj1 positive neurons or reversing the suppression effect of Aβ on neurogenesis by lithium chloride, kenpaullone, SB-216763, indirubin-3'-monoxime, or by siRNA (SEQ ID NOs: 15-17) to inhibit the expression of GSK-3β, does not reasonably provide enablement for a method of the manufacture of all types of neurons comprising culturing a neural stem cell in the presence of all substances that inhibits all activities of GSK-3 as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

"There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue'. These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)". See MPEP § 2164.01.

Claim 38 is directed to a method of the manufacture of a neuron comprising culturing a neural stem cell in the presence of a substance that inhibits the activity of GSK-3 to allow neurogenesis in cultures. Applicant describes a cell culture condition for adult neural stem cells, ANSC-7 cells, which is to isolate cells from the region of adult ventricle cortex and culture the isolated cells in a medium comprising DMEM/F12 and 10% fetal bovine serum (FBS) and further in a medium comprising DMEM/F12, 1%N2 supplement, 20ng/ml FGF, and plate the cells on dishes coated with laminin and

polyornithine. Applicant further demonstrates that the differentiation of ANSC-7 is induced by lithium chloride as analyzed by a neuronal marker, β-III-tubulin, using an anti-Tuj1 (β-tubulin III) antibody. In addition, the neurogenesis of ANSC-7 is suppressed by Aβ peptides and the suppressing effect of Aβ can be inhibited by the molecules that inhibit the activity of GSK-3β, including lithium chloride, kenpaullone, SB-216763, indirubin-3'-monoxime or siRNA of GSK-3 (SEQ ID NOs: 15-17).

Based on the specification and prior art, Applicant is enabled for manufacturing neurons with anti-Tuj1 positive from neural stem cells by lithium chloride, kenpaullone,SB-216763, indirubin-3'-monoxime or siRNA of GSK-3β (SEQ ID NOs: 15-17) or other known GSK-3β inhibitors that could promote neurogenesis, such as anti-GSK-3β antibody. It is known in the art that GSK-3 contains two isoforms –α and –β as described in the specification. However, the claim is not limited to using the inhibitors of GSK-3β as set forth above. The specification describes the inhibitors of GSK-3 including siRNA (SEQ ID NOs: 15-17) and several compounds with formulas and potential substitutions on p.7-38, 43-53. The specification also describes the inhibitors of GSK-3β including peptides and proteins and cell extracts etc. (on p.56) and they are not limited to the substance as set forth above. Applicant fails to teach what other inhibitors of GSK-3β could be used in the claimed method since the disclosure fails to set forth the characteristics of other inhibitors of GSK-3β that could be used in the claimed method. It is unknown what specific peptides or proteins could be used as inhibitors of GSK-3β. Furthermore, it is also unpredictable whether all the compound derivatives as described in the specification (p. 7-38, 43-53) could be used in the claimed method since the

specification fails to teach how to make/use all the listed compounds. It may also require different techniques to synthesize different compounds and test whether they could function as an inhibitor of GSK-3β to allow neurogenesis of neural stem cells as in the claim since different inhibitors of GSK-3β could inhibit different activities of GSK-3 on different substrates.

The claim is also not limited to generating Tuj1 positive neurons. There are different neuronal cell types with different functions such as excitatory neurons and inhibitory neurons including dopaminergic, glutamatergic, serotonergic, cholinergic, GABAergic neurons and other neurotransmitter specific neurons. It is not known what specific neurons would be obtained in the instant method because β-III tubulin (anti-Tuj1) is considered as a neuronal marker that is expressed in all neuronal precursor/progenitor cells and mature neurons. Applicant fails to teach whether the culture conditions as set forth in the specification could be applied to all types of neural stem cells that could be derived embryonic stem cells and from all different regions of the central nervous systems or other systems since the cell lineages derived from embryonic stem cells or different brain regions would differentiate differently (see p. 385, the section of Cell lines derived by oncogene expression, Gottlieb. Annu. Rev. Neurosci. 2002. 25: 381-407). Applicant fails to teach whether all different types of neural stem/precursor cells derived from different cell origins/brain regions cultured in the conditions as in the claimed method could still maintain the characteristics to differentiate into a specific population of neurons since embryonic neural tissues or other neural stem cells with different origins in neural cultures have not been fully

characterized. The embryonic neural tissues contain very diverse cell types including multipotent progenitor cells, restricted neuronal progenitor, and restricted glial progenitor cells (see p. 385, the section of Cell lines derived by oncogene expression, Gottlieb. Annu. Rev. Neurosci. 2002. 25: 381-407). The control and regulation of cell lineages are still not understood. In addition, the embryonic stem cells derived from all different brain regions or different systems contain very diverse cell types. Each type of embryonic stem cells has its unique biochemical properties. It is unpredictable whether they are able to differentiate into a specific population of neurons after expanding and culturing with the conditions described in the specification because it depends on the niche or environmental cues for these embryonic stem cells (see p. 143-144, the section of Embryonic stem cells, Fuchs et al. Cell. 2000. 100: 143-155). Therefore, it is unpredictable whether the cells expanded from embryonic stem cells and cells expanded from neural precursor cells still have the ability of differentiation into a specific population of neurons. Furthermore, the cell lineage and characteristics of other cell origins or brain regions that potentially contain neural stem cells have not been characterized. The phenotypes of each cell type are not clear after they are expanded in a culture medium. The expanded embryonic neural stem cells and expanded neural stem/precursor cells still have potentials to develop into the cell lineage other than neural cells or neurons. Thus, it is unpredictable whether the cells expanded from these different origins/brain regions still have the potential to maintain the capability of differentiation into neurons. The instant specification has not provided sufficient guidance as to enable one of skill in the art to enhance neurogenesis from any neural

stem cells derived from different cell origins or brain regions in the presence of an inhibitor of GSK-3 without undue experimentation. One of skill in the art would need to further characterize embryonic stem cells or neural stem/precursor cells derived from different cell origins/brain regions, and then understand whether the culture system can be used to expand and differentiate these different types of cells into a specific population of neurons.

Claim 38 is also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

Claim 38 is directed to a method of the manufacture of a neuron comprising culturing a neural stem cell in the presence of the substance that inhibits the activity of GSK-3. The claim recites "the substance" used in the claimed method. Although the specification describes the inhibitors of GSK-3 including siRNA (SEQ ID NOs: 15-17) and compounds with formulas and potential substitutions on p.7-38, 43-53 and peptides

and proteins and cell extracts etc (on p.56), the specification fails to limit the substance that could be used in the claimed method. In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicant has possession of and what Applicant is claiming. From the specification, it is clear that Applicant has possession of lithium chloride, kenpaullone, SB-216763, indirubin-3'-monime or siRNA (SEQ ID NOs: 15-17) that can be used in the claimed method as described on p. 86 of the specification. However, the claims are not limited to the compounds as set forth above. The specification only describes lithium chloride, kenpaullone, SB-216763, indirubin-3'-monime or siRNA that can be used in the claimed method to promote neurogenesis in cultured ANSC-7 cells. Although Applicant also describes several species that could potentially be used in the claimed method, Applicant fails to describe what other specific common structures/characteristics are required for the substance to inhibit the activity of GSK-3 and to allow neurogenesis from neural stem cells. Thus, it is unknown what other specific structures/characteristics are required to maintain the ability of inhibitors of GSK-3□ to allow neurogenesis from neural stem cells in cultures as in the claimed method. Since other common structures/characteristics of the substances are unknown, a skilled artisan cannot contemplate the functional correlations between the claimed genus and the claimed method. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the genus of proteins.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, a method of the manufacture of a neuron comprising culturing a neural stem cell in the presence of the substance that inhibits the activity of GSK-3. has not met the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 38 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 38 is indefinite because Applicant recites "activity" in the claim. Although Applicant describes phosphorylation of tau and protecting neuronal cell death by GSK-3 on p.5, this description is not definite; there is no limitation on what would or would not be considered as an "activity" and thus be within the scope of the claims. In addition, claim 38 is indefinite because the recitation "the substance". Although the specification describes the inhibitors of GSK-3 including siRNA (SEQ ID NOs: 15-17) and compounds with formulas on p.7-38, 43-53 for the potential small molecule inhibitors of GSK-3, the specification also describes that the substance are not limited to peptides, proteins, cell extracts and the molecules and compounds as set forth above (p. 56). The disclosure fails to set forth the metes and bounds of what is encompassed within the definition of such analogs and derivatives and thus the claims are indefinite.

In addition, claim 38 recites the limitation "the manufacture " in line 1, "the substance" in line 2 and "the activity" in line 3 of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 38 is rejected under 35 U.S.C. 102(b) as being anticipated by WO03/004485 (PCT/JP02/06776, published on Jan 16, 2003, filed on Jul 4, 2002 as evidenced by US 2004/0167171 (published on Aug 26, 2004, which is a 371 of WO03/004485 (PCT/JP02/06776)).

US 2004/0167171 teaches a method of enhancing neurogenesis in a neural cell cultures in the presence of a substance that inhibits the activity of GSK-3β as in claim 38 (see p. 153). '171 teaches several inhibitors of GSK-3β including SB-216763 (see p. 42, 1st col, line 39; p. 159 claims 49-66). '171 teaches a method of enhancing neuronal differentiation from cells isolated from 2 day old rat cerebral cortex in a culture medium in the presence of an inhibitor of GSK-3β as described in the instant specification (see p.153, [1252]-[1259]). The differentiated neurons were detected by an anti-β-III tubulin antibody, which is the same as used in the instant specification (see p. 153, [1255]-[1256]). Thus, claim 38 is anticipated by WO03/004485.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 38 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6040180 (issued on Mar 21, 2000) in view of Chen et al. (J. Neurochem. 2000. 75: 1729-1734 as in IDS) and Cross et al. (J. Neurochem. 2001. 77:94-102 as in IDS).

US Patent No. 6040180 teaches a method of culturing neural stem cells and differentiating neural stem cells into neurons by growth factor. '180 teaches generating neurons from neural stem cells that isolated from either embryonic or adult brains by stimulating these neural stem cells with BDNF (see col. 15-18, lines 14-62; col. 35-36, claims 1-6). The brain regions for isolating neural stem cells include hippocampus (see col.15-17). '180 fails to teach the substance that inhibits the activity of GSK-3. The

teachings of '180 provide guidance on a method of differentiating neural stem cells to neurons.

Chen et al. teach that lithium can enhance neurogenesis in the adult hippocampus (see p. 1729, abstract). In addition, lithium is an inhibitor of GSK-3□ as evidenced by Eldar-Finkelman (see p. 130, 2nd col. 2nd paragraph. Trends in Mol. Med. 2002. 8:126-132).

Cross et al. teach several small-molecule inhibitors of GSK-3, SB-415286 and SB-216763 can protect neuronal cell death in primary neuronal cultures of the peripheral nervous system and central nervous system (see p. 94, abstract). The teachings of Cross et al. suggest that SB-415286 and SB-216763 are inhibitors of GSK-3β and can be used to protect neuronal cell death.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to use an inhibitor of GSK-3β, such as lithium and SB-216763 to enhance neurogenesis of Tuj1 positive neurons from neural stem cells. The person of ordinary skill in the art would have been motivated to do so because it has been shown that lithium can induce neurogenesis in the hippocampus and SB-216763 and lithium are inhibitors of GSK-3β. One of ordinary skill in the art would have expected success in generating neurons by incubating neural stem cells with an inhibitor of GSK-3β such as lithium or SB-216763.

Conclusion

NO CLAIM IS ALLOWED.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

WO02/062387 (PCT/GB02/00542, published on Aug 15, 2002, as in IDS submitted on Oct 4, 2005.).

WO99/42100 (EP1057484, published Aug 26, 1999 as in IDS).

US2004/0247525 (published Dec 9, 2004, filed on Jan 22, 2004, priority date Jan 23, 2003).

Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang, Ph.D. whose telephone number is

(571) 272-4521. The examiner can normally be reached on Monday-Thursday and every other Friday from 8:30 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CYW
January 16, 2007

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER